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Potassium-competitive acid blockers: Advanced therapeutic option for acid-related diseases

Nobuhiro Inatomi^a, Jun Matsukawa^{a,*}, Yuuichi Sakurai^b, Kazuyoshi Otake^c^a Pharmaceutical Research Division, Takeda Pharmaceutical Company Limited, Fujisawa, Kanagawa 251-8555, Japan^b Japan Development Center, Takeda Pharmaceutical Company Limited, Chuo-ku, Osaka 540-8645, Japan^c Global Medical Affairs Japan Department, Takeda Pharmaceutical Company Limited, Chuo-ku, Tokyo 103-8668, Japan

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ABSTRACT

Acid-related diseases (ARDs), such as peptic ulcers and gastroesophageal reflux disease, represent a major health-care concern. Some major milestones in our understanding of gastric acid secretion and ARD treatment reached during the last 50 years include 1) discovery of histamine H₂-receptors and development of H₂-receptor antagonists, 2) identification of H⁺,K⁺-ATPase as the parietal cell proton pump and development of proton pump inhibitors (PPIs), and 3) identification of *Helicobacter pylori* (*H. pylori*) as the major cause of peptic ulcers and development of effective eradication regimens. Although PPI treatments have been effective and successful, there are limitations to their efficacy and usage, i.e. short half-life, insufficient acid suppression, slow onset of action, and large variation in efficacy among patients due to CYP2C19 metabolism. Potassium-competitive acid blockers (P-CABs) inhibit H⁺,K⁺-ATPase in a reversible and K⁺-competitive manner, and exhibit almost complete inhibition of gastric acid secretion from the first dose. Many pharmaceutical companies have tried to develop P-CABs, but most of their clinical development has been discontinued due to safety concerns or a similar efficacy to PPIs. Revaprazan was developed in Korea and was the first P-CAB approved for sale. Vonoprazan, approved in 2014 in Japan, has a completely different chemical structure and higher pK_a value compared to other P-CABs, and exhibits rapid onset of action and prolonged control of intragastric acidity. Vonoprazan is an effective treatment for ARDs that is especially effective in healing reflux esophagitis and for *H. pylori* eradication. P-CABs, such as vonoprazan, promise to further improve the management of ARDs.

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1. Introduction

Gastric acid is important for the sterilization of food and water and for digestion. Gastric acid secretion is a complex process that involves neuronal, hormonal, and endocrine pathways, all of which have one common target: the parietal cell. The parietal cell is responsible for secreting concentrated hydrochloric acid into the gastric lumen. The empirical realization that peptic ulcer disease (PUD) only occurred in the presence of gastric acid (Schwartz, 1900) led to the dictum of “no acid, no ulcer”. Acid is also considered of central importance in the initiation and continuation of gastroesophageal reflux disease (GERD), nonsteroidal anti-inflammatory drug (NSAID) associated upper gastrointestinal damage, and ulceration in hypersecretory conditions such as Zollinger–Ellison syndrome. Many patients with these diseases benefit

from acid-suppressive therapy, supporting the importance of gastric acid in the pathogenesis of these diseases.

Since the isolation of *Helicobacter pylori* (*H. pylori*) more than 30 years ago (Marshall & Warren, 1984), our understanding of the pathogenesis of gastroduodenal diseases has changed dramatically. Many diseases related to *H. pylori*, such as peptic ulcer and mucosal associated lymphoid tissue lymphoma, are curable, and gastric cancer might even be preventable, by the implementation of *H. pylori* eradication therapy (Malfertheiner et al., 2014). The incidence of PUD in the Western hemisphere and Japan has decreased in the past few decades, probably due to decreased infection rates with *H. pylori*. However, over the same period, the incidence of GERD has increased dramatically and GERD has become a major gastric acid-related disease (ARD).

The healing of duodenal ulcers, gastric ulcers and GERD with acid suppressants is highly correlated with control of gastric acid secretion (Burget et al., 1990; Howden et al., 1991; Bell et al., 1992). The goals of treatment for these diseases are to heal established lesions, relieve symptoms, and to prevent recurrence and complications. A meta-analysis has shown that maintaining intragastric pH at 3 or above for 18 to 20 h a day is optimal for healing duodenal ulcer (Howden et al., 1994). In patients with reflux esophagitis, an intragastric pH of 4 or

Abbreviations: ARD, acid-related disease; CCK₂R, cholecystokinin-2 receptor; ECL, enterochromaffin-like; H₂RA, histamine H₂ receptor antagonist; *H. pylori*, *Helicobacter pylori*; GERD, gastroesophageal reflux disease; M₃R, muscarinic M₃ receptor; P-CAB, potassium-competitive acid blocker; PPI, proton pump inhibitor; PUD, peptic ulcer disease.

* Corresponding author at: Extra Value Generation Drug Discovery Unit, Pharmaceutical Research Division, Takeda Pharmaceutical Company Limited, Japan.

E-mail address: jun.matsukawa@takeda.com (J. Matsukawa).

above has been shown to be the standard target for treatment (Hunt, 1999). Current *H. pylori* eradication therapy uses at least 2 antibiotics, such as amoxicillin and clarithromycin, and also requires administration of acid suppressant to elevate intragastric pH to 5 or above to promote *H. pylori* transition from a stationary phase to a growth phase, which leaves the bacteria susceptible to antibiotics (Sachs et al., 2011). The quest for better therapies has pushed research towards new acid-suppressive agents and formulations (Scarpignato & Hunt, 2015). This review examines the development and issues associated with current ARD treatments, with a particular focus placed on potassium-competitive acid blockers (P-CABs) which promise to be the most effective acid suppressant to date.

2. Mechanisms of gastric acid secretion

The parietal cell of the gastric gland is a highly differentiated cell responsible for secreting concentrated hydrochloric acid into the gastric lumen. Gastric acid secretion can occur upon ingestion of food or drink, or be stimulated by the thought, smell, or taste of food. Such direct and indirect parietal cell stimulation is mediated by 3 types of receptor: cholinergic muscarinic M_3 receptors (M_3R), histamine H_2 -receptors (H_2R), and cholecystokinin-2/gastrin receptors (CCK_2R). Histamine, produced in enterochromaffin-like (ECL) cells by the decarboxylation of L-histidine by histidine decarboxylase, is thought to play a central role as a stimulant of gastric acid secretion by binding to H_2R . H_2R activation causes an increase in intracellular cyclic AMP levels, which serves as a second messenger that transfers the signal to the final step of acid secretion, i.e. H^+, K^+ -ATPase (Ganser & Forte, 1973; Soll & Wollin, 1979). In contrast, stimulation of either M_3R by acetylcholine or CCK_2R by gastrin results in a signal mediated by an intracellular increase in free Ca^{2+} ions. Gastrin mediates acid secretion primarily by stimulating the release of histamine from neuroendocrine ECL cells after binding to CCK_2R . There has been some debate over whether activation of the parietal cell CCK_2R leads to acid secretion (Hinkle et al., 2003; Dufresne et al., 2006), and it seems the intracellular concentration of cyclic AMP must first be above a threshold level before gastrin can directly stimulate the parietal cell (Soll, 1982; Geibel et al., 1995). Activation of these receptors stimulates H^+, K^+ -ATPase (Sachs et al., 2014).

H^+, K^+ -ATPase belongs to the family of P_2 -type ATPases, which includes the ubiquitous Na^+, K^+ -ATPase and sarcoplasmic reticulum Ca^{2+} -ATPase. H^+, K^+ -ATPase assembles as a heterodimer comprised of one catalytic α and one β subunit, which share a significant degree of sequence homology with the corresponding subunits of Na^+, K^+ -ATPase. The H^+, K^+ -ATPase α subunit contains about 1035 amino acids (Maeda et al., 1988) and the β subunit contains about 290 amino acids (Hall et al., 1990; Reuben et al., 1990). The H^+, K^+ -ATPase α subunit has 10 transmembrane segments and the β subunit has 1 transmembrane segment. The α subunit contains the catalytic site and is responsible for ion exchange between the gland lumen and parietal cell cytosol, while the β subunit is essential for stabilization of the α subunit. The extracellular domain of the β subunit contains multiple N-glycosylation sites, which are not only necessary for targeted membrane trafficking, but also for correct heterodimer assembly (Asano et al., 2000; Vagin et al., 2003). In the resting parietal cell, H^+, K^+ -ATPase is found in smooth-surfaced cytoplasmic tubulovesicles. Upon stimulation, H^+, K^+ -ATPase is moved to apical microvilli of the secretory canaliculi of the parietal cell (Yao & Forte, 2003; Forte & Zhu, 2010). Along with H^+, K^+ -ATPase, the K^+ -channel $KCNQ1/KCNE2$ complex and a Cl^- channel are also moved (Lambrecht et al., 2005; Nguyen et al., 2013). This morphological change results in a several-fold expansion of the secretory canaliculi (Helander & Hirschowitz, 1972). H^+, K^+ -ATPase catalyzes an electroneutral exchange of cytoplasmic protons for extracytoplasmic potassium by means of conformational changes that occur by MgATP-driven phosphorylation and dephosphorylation of the α subunit (Sachs et al., 1976). Activation of K^+ and perhaps Cl^- conductance in the H^+, K^+ -ATPase membrane allows K^+ to access the

extracytoplasmic face of the pump, which enables dephosphorylation and recycling of the pump (Wolosin & Forte, 1983). H^+, K^+ -ATPase conformations that bind ions for outward transport are termed E_1 conformations, and conformations that bind luminal ions for inward transport are termed E_2 conformations. As a member of the P_2 -type ATPase family, the H^+, K^+ -ATPase enzyme cycle involves switching between E_1 and E_2 -P states (Fig. 1). Hydronium ion binding to the cytoplasmic surface of the E_1 form of H^+, K^+ -ATPase activates phosphorylation by MgATP to form the intermediate E_1 -P, which then converts to E_2 -P in the acid transporting step. After release of H_3O^+ and binding of K^+ on the extracytoplasmic surface of the enzyme, the E_2 - PK^+ conformation is formed. The E_2 - PK^+ conformation then converts to the E_1K^+ conformation after dephosphorylation. The E_1K^+ conformation releases K^+ to the cytoplasmic side, allowing rebinding of H_3O^+ and completing the enzyme cycle. At neutral pH, $2H^+$ are exchanged for $2K^+$ per hydrolysis of 1 ATP, but as the luminal pH falls, the exchange stoichiometry becomes $1H^+$ exchanged for $1K^+$ per 1 ATP. This stoichiometry change is explained by the pKa of one of the hydronium binding sites, which remains protonated at luminal pH < 3.0 (Rabon et al., 1982). H^+, K^+ -ATPase exists as an $(\alpha\beta)_2$ heterodimeric dimer (Shin & Sachs, 2006).

When active acid secretion ceases, parietal cells revert to a resting conformation to prepare for the next stimulation (Forte et al., 1977). Based on the membrane recruitment and recycling hypothesis, withdrawal of stimulus leads to a progressive resequestration of the expanded apical membrane and H^+, K^+ -ATPase is taken back into the cytoplasmic tubulovesicles. The proton pump protein has a half-life of about 54 h in rats (and probably similar in humans), thus about 20% of pumps are synthesized anew over 24 h (Shin & Kim, 2013).

It has been suggested that gastric H^+, K^+ -ATPase is present at sites other than the stomach e.g., the cortical collecting duct of the kidney (Kraut et al., 2001), rat vascular smooth muscle cells (McCabe & Young, 1992), human leukocytes (Ritter et al., 1998), and rat cardiac myocytes (Beisvag et al., 2003). However, Herrmann et al. (2007) clearly demonstrated, using quantitative mRNA analysis, western blot, and immunohistochemistry, that the stomach is the only organ in humans that expresses significant levels of mRNA and protein of both the α - and β -subunits of gastric H^+, K^+ -ATPase.

3. Antacids and receptor antagonists

Pharmacotherapy for PUD has comprised largely ineffective approaches that included antacids and anticholinergics. Antacids, such as sodium bicarbonate, aluminum hydroxide, magnesium hydroxide and calcium carbonate, have come into widespread use, especially in association with a strict Sippy-type bland diet (Sippy, 1983). Antacids provide a degree of symptom relief by neutralizing intragastric acid, but their

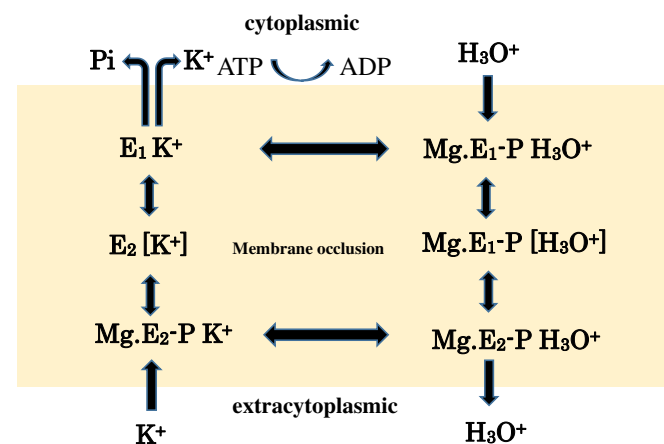


Fig. 1. The catalytic cycle of gastric H^+, K^+ -ATPase.

effective duration is too short for healing of erosions or ulcers (Feurle, 1975). Anticholinergic agents (non-selective muscarinic receptor antagonists) were also put to limited use since they were relatively weak inhibitors at therapeutic doses and had many side effects such as dry mouth, blurred vision, tachycardia, and bladder dysfunction (Mejia & Kraft, 2009). Currently, no selective M_3 antagonists are available for clinical use. Selective M_1 R antagonists, such as pirenzepine and telenzepine, have been used clinically since their side effects are less frequent. Although pirenzepine produces slight inhibition of basal, stress, and meal-stimulated acid secretion at doses of 50 to 100 mg, H_2 R antagonists (H_2 RAs) inhibit acid secretion more effectively than pirenzepine (Fiorucci et al., 1988). Pirenzepine also inhibits muscarinic receptors outside the stomach, causing side effects such as dry mouth and blurred vision at higher doses. Ash and Schild (1966) clearly demonstrated that histamine receptors expressed in the stomach or uterus are different from those in the ileum, and concluded that at least two classes of histamine receptors exist. Black et al. (1972) of Smith, Kline & French (now GlaxoSmithKline) succeeded in developing burimamide, the first H_2 RA. Burimamide was not potent enough for oral administration, and structural modifications intended to change the acid dissociation constant of burimamide, led to the development of metiamide. Metiamide was an effective agent, but was associated with unacceptable nephrotoxicity and agranulocytosis. It was proposed that this toxicity arose due to the thiourea group in metiamide, and so other, similar guanidine analogs were investigated. This led to the discovery of cimetidine, the first clinically successful H_2 RA (Brimblecombe et al., 1975). Cimetidine was approved in 1976 in the UK and in 1977 in the USA. By modifying the chemical structure of cimetidine, Glaxo (also now GlaxoSmithKline) developed ranitidine and Yamanouchi (now Astellas Pharma) developed famotidine. Ranitidine and famotidine were found to have a far-improved tolerability profile (i.e. fewer adverse drug reactions), longer-lasting action, and be more potent than cimetidine. The discovery of H_2 RAs revolutionized PUD therapy. H_2 RAs offer several advantages over antacids, including longer duration of action, greater efficacy, and the ability to be used prophylactically as well as for symptom relief. However, several shortcomings of H_2 RAs became apparent. Firstly, because of their limited duration of action, patients needed to take 2 or 3 doses each day. Secondly, H_2 RAs induce tachyphylaxis/tolerance after several days of treatment. Thirdly, their effect on meal-stimulated acid secretion is limited as compared to their effect on basal acid secretion at night. Furthermore, their efficacy in relieving GERD symptoms and eradicating *H. pylori* is mostly inadequate (Sachs et al., 2014).

Several high affinity CCK_2 R antagonists, such as YM-022 (Nishida et al., 1994), RP-73870 (Pendley et al., 1995), S-0509 (Takeuchi et al., 1999), YF-476 (Takinami et al., 1997) and spiroglumide (Scarpignato et al., 1996) have been evaluated and shown to reduce gastric acid secretion. YF-476, the gold standard of this class, inhibited gastric acid secretion for longer than ranitidine (Boyce et al., 2012). However, the development of this compound was stopped after its ability to inhibit acid secretion was found to decline over several days (Steel, 2002). The development of other compounds was also suspended.

4. Proton pump inhibitors

The French pharmaceutical company Servier reported strong antisecretory activities for thioacetamide derivatives (coded by Servier as CMN 131; Malen & Danree, 1971), but development of these compounds was not pursued as they produced strong acute toxicity in animals. The antisecretory activity of CMN 131 prompted AB Hässle to start looking for structural analogs that did not cause acute toxicity. Scientists at AB Hässle speculated that the toxicity might originate from a thioamide group, so they eliminated the thioamide group and added a benzimidazole ring. Finally, a sulfide was modified to a sulfoxide due to a conflicting preexisting patent, and timoprazole was synthesized (Olbe et al., 2003). Subsequent toxicological studies of timoprazole

revealed that it caused enlargement of the thyroid gland. Other derivatives were screened and picoprazole was found to have strong antisecretory activity without the toxicological effects of timoprazole seen in the thyroid/thymus. Scientists at AB Hässle also found that picoprazole, unlike H_2 RAs, inhibited acid secretion independently of stimulus. This effect was thought to be due to inhibition of H^+ , K^+ -ATPase, indicating that picoprazole was a new class of antisecretory compound (Fellenius et al., 1981). Binding studies with substituted benzimidazoles showed that specific binding to H^+ , K^+ -ATPase occurred in the secretory canaliculi of parietal cells. Substituents on the heterocyclic ring were modified and a compound was obtained with a weak base at the site of action. This compound, synthesized in 1979, was given the generic name of omeprazole, and was developed as the world's first PPI (Lundell, 2015).

In the late 1960s, Takeda Pharmaceuticals also discovered that 2-pyridylthioacetamide (coded by Takeda as AG-35) and its analogs exhibited a strong antisecretory and antiulcer activity in animals during screening for antiulcer drugs (Kanno et al., 1973), and the company applied for a Japanese patent for the compounds as novel antiulcer drugs (Kanai et al., 1969). AB Hässle's findings regarding novel mechanisms of antisecretory action motivated Takeda to screen for antisecretory drugs. Takeda screened more than 700 compounds in searching for a new acid suppressant with a chemical structure that differed from timoprazole, but eventually recognized the basic structure of timoprazole was essential (Satoh, 2013). Takeda investigated various modifications of timoprazole and eventually found that the introduction of fluorinated substituents, such as a trifluoroethoxy group, to timoprazole markedly improved the antiulcer properties of the compound, which resulted in the discovery of lansoprazole (Kubo et al., 1990). Substituted benzimidazoles such as pantoprazole and rabeprazole were also developed. Tenatoprazole has an imidazopyridine ring instead of a benzimidazole ring and a plasma half-life of about 7 h, which is longer than that of benzimidazole-based PPIs (Sachs et al., 2006). However, tenatoprazole has not yet been approved for marketing and sale. Omeprazole is a racemic mixture of two enantiomers, R-omeprazole and S-omeprazole, that show different affinities for cytochrome P450 (CYP) enzymes. The plasma level of S-omeprazole (esomeprazole) is better than R-omeprazole because the R-enantiomer is more sensitive to CYP2C19 than S-omeprazole (Abelö et al., 2000; Andersson et al., 2001). Like omeprazole, lansoprazole is also a racemate, though its R- and S-enantiomers were shown to have equal pharmacological activity (Nagaya et al., 1991). However, unlike omeprazole, the R-enantiomer (dexlansoprazole) of lansoprazole was shown to be less sensitive to CYP enzymes. A novel dual release formulation of dexlansoprazole consisting of a normal enteric coating release at pH 5.5 (pH in upper intestine) and a coating release at pH 6.75 (pH in lower intestine) extended the duration of dexlansoprazole in the blood (Emerson & Marzella, 2010). Dexlansoprazole also allows flexible dosing such that administration of the drug could be independent of timing of food intake (Lee et al., 2010). In a clinical study, 60 mg of this dual release formulation of dexlansoprazole resulted in a higher intragastric pH than 40 mg of esomeprazole (Kukulka et al., 2011). The canaliculus of the parietal cell is the only membrane-enclosed space in the body with a pH below 4.0. All PPIs are lipophilic and weak bases with pK_a values of 3.8 to 5.0. They easily penetrate cell membranes and are accumulated in the highly acidic parietal cell canaliculi as a result of protonation of the pyridine moiety, which renders them less permeable (Sachs et al., 2014). A second protonation of the benzimidazole ring causes a chemical rearrangement involving nucleophilic attack of the pyridine ring, producing a planar cationic sulfenic acid (Lindberg et al., 1986; Nagaya et al., 1989). This sulfenamide form produced by dehydration of the sulfenic acid is the active form of PPIs. It reacts with cysteine sulfhydryls on H^+ , K^+ -ATPase to form covalent disulfide bonds that inhibit pump activity.

PPIs are weak bases with a pK_a value of around 4.0 that allows their selective accumulation in the secretory canaliculus of the parietal cell. Whole body autoradiography of a mouse injected intravenously with

tritiated omeprazole showed general labeling after 5 min, but after several hours labeling was found only in the stomach (Helander et al., 1985). Higher magnification showed that labeling was present only in parietal cells (Scott et al., 1994), and a radioautographic study of ^3H -labeled lansoprazole revealed that most silver grains were found in the cytoplasmic canaliculi (Sekiguchi et al., 1992). These findings suggest that lansoprazole accumulates in parietal cells, and its binding is covalent. The binding location of radioactive PPIs on H^+,K^+ -ATPase revealed one or more cysteine(s) that were critical for inhibition of enzyme activity. Full inhibition was obtained by lansoprazole labeling of Cys321, Cys813 or Cys822, and Cys892 (Sachs et al., 1993), omeprazole labeling of Cys813 or Cys892 and slight labeling of Cys892 (Besancon et al., 1993), and pantoprazole labeling of Cys813 and Cys822 (Shin et al., 1994). All active forms of all PPIs react with Cys813, which is located in a luminal vestibule of H^+,K^+ -ATPase. This reaction results in covalent inhibition of the enzyme via formation of a disulfide bond that stabilizes the enzyme in its E_2 conformation. The covalent binding of PPIs with H^+,K^+ -ATPase allows a duration of action far longer than their plasma half-life. PPIs are metabolized by the CYP system. The principal enzyme of their metabolism is CYP2C19, with CYP3A4 also being involved. The CYP2C19 gene is mutated in approximately 3% of Caucasians and 13% to 22% of East Asians, resulting in PPIs having relatively poor clearance (Furuta et al., 2005). CYP2C19 genotypes are classified into three groups: homozygous extensive metabolizer (HomEM), heterozygous EM (HetEM), and poor metabolizer (PM). Plasma PPI levels and intragastric pHs during PPI treatment are lowest in the HomEM group, higher in the HetEM, and highest in the PM group. These CYP2C19 polymorphisms influence the pharmacokinetics and pharmacodynamics of PPIs (Shirai et al., 2002). CYP2C19 genotype is a crucial factor in determining the efficacy of *H. pylori* eradication in patients taking PPI-based triple therapies (Kuo et al., 2014). Clopidogrel is an antiplatelet agent and inactive prodrug that is mainly converted to its active metabolite via CYP2C19. Because of this, the Food and Drug Administration has warned against using certain PPIs in patients receiving clopidogrel. Lansoprazole, dexlansoprazole, pantoprazole-Na, and rabeprazole appear to be associated with lower incidences of drug interactions compared to omeprazole and esomeprazole (Frelinger et al., 2012; Wedemeyer & Blume, 2014). However, a randomized controlled trial that compared clopidogrel alone with combination therapy of clopidogrel and omeprazole found no increase in adverse cardiovascular outcomes, and observed that PPI co-therapy reduced the risk of new adverse gastrointestinal outcomes (Bhatt et al., 2010).

Although PPIs have been very successful and effective, they also possess a number of limitations, such as less than complete gastric acid suppression (especially at night), interpatient variability in efficacy due to CYP2C19 metabolism, and the inconvenience of requiring mealtime dosing to ensure adequate levels of the drug during periods of H^+,K^+ -ATPase activity. In addition, PPIs are slow to achieve steady state inhibition of gastric acid secretion, typically taking 3 to 5 days to achieve maximum inhibition (Piche & Galmiche, 2005; Sachs et al., 2006). The slow onset of action of PPIs results from the continuous switching of H^+,K^+ -ATPase from an inactive to active state, the need for PPI accumulation and activation in the parietal cell, and the short plasma half-life (about 1.5 h) of PPIs (Hatlebakk & Berstad, 1996; Sachs, 2001). A PPI can only inhibit H^+,K^+ -ATPase that is actively secreting at the surface of the secretory canaliculus of the parietal cell. Although any H^+,K^+ -ATPase with a covalently bound PPI will remain inactive unless inhibition is reversed by a cellular reducing agent such as glutathione, newly synthesized H^+,K^+ -ATPase or those activated after the plasma concentration of the PPI has fallen below threshold will not be inhibited. The short plasma half-life of PPIs allows rapid restoration of gastric acid secretion by uninhibited, restored, or new proton pumps. Consequently, for GERD patients, more complete and faster relief of symptoms is still needed (Kleinman et al., 2002). In about two thirds of symptomatic GERD patients, reflux symptoms are not adequately controlled by an initial dose of PPI, with nearly 50% of patients still suffering from symptoms

3 days later (Yuan et al., 2008; Hunt & Scarpignato, 2015). Approximately one-third of GERD patients report persistent symptoms and are dissatisfied with PPI therapy (Chey et al., 2010). One strategy to improve PPI therapy has been to prolong the plasma dwell time of PPIs. Alevium (AGN201904-Z), made by Alevium Pharmaceuticals, is a prodrug form of omeprazole that is slowly absorbed throughout the intestine, resulting in a longer plasma dwell time compared to other PPIs. Alevium at 600 mg showed a more prolonged acid-suppressive effect than esomeprazole at 40 mg in healthy volunteers (Hunt et al., 2008), though there has been no further clinical development of this compound. Another strategy to prolong blockage of H^+,K^+ -ATPase was to develop drugs more resistant to metabolism, such as esomeprazole and dexlansoprazole. However, despite several years of extensive research and advances in our understanding of PPIs, their limitations still remain (Sachs et al., 2010). While PPI limitations are mainly related to their shared mechanism of action, these new drugs represented a measurable but only incremental advance in control over gastric acid secretion compared to conventional PPIs, so it was logical that other potential approaches would be considered. A more innovative approach has been the development of potassium-competitive acid blockers (Andersson & Carlsson, 2005).

5. Potassium-competitive acid blockers

5.1. Development of potassium-competitive acid blockers

In the early 1980s, an imidazopyridine compound, SCH28080, was developed by Schering-Plough that inhibited gastric acid secretion in animals and humans (Ene et al., 1982; Chiu et al., 1983). SCH28080 inhibited the acid response to histamine, high K^+ , methacholine, and cyclic AMP. Kinetic studies indicated competitive inhibition of H^+,K^+ -ATPase by SCH28080 with respect to K^+ , suggesting a competitive interaction with the high affinity K^+ -site of H^+,K^+ -ATPase (Beil et al., 1986). However, clinical development of SCH28080 was stopped because repeated administration caused hepatic toxicity. This initiated studies of a series of SCH28080 derivatives. Imidazopyridine derivatives (e.g., linaprazan and BY841), imidazonaphthyridine derivatives (e.g., soraprazan), imidazothienopyridines (e.g., SPI-447), quinolone derivatives (e.g., SK&F96067 and SK&F97574), pyrrolopyridazine derivatives (e.g., CS-526), pyrimidine derivatives (e.g., revaprazan) and pyrrole derivatives (e.g., vonoprazan) were developed (Wallmark et al., 1987; Keeling et al., 1991; Wurst & Hartmann, 1996; Tsukimi et al., 2000; Park et al., 2003; Gedda et al., 2007; Hori et al., 2010). Such compounds that compete with K^+ binding and inhibit gastric acid secretion are called potassium-competitive acid blockers (P-CABs), or acid pump antagonists. The chemical structures of SCH28080, soraprazan, revaprazan, linaprazan (AZD0865), and vonoprazan (TAK-438) are shown in Fig. 2. Among these compounds, revaprazan and vonoprazan were developed for clinical use, approved, and now used as therapeutics for the treatment of ARDs. Revaprazan was launched in South Korea in 2007 by Yuhan Corporation for the treatment of duodenal ulcer, gastric ulcer and gastritis, and is also available in India. Vonoprazan was first launched in Japan in 2015 by Takeda Pharmaceuticals for the treatment of gastric ulcer, duodenal ulcer, erosive esophagitis, prevention of low dose aspirin- or NSAID-induced ulcer recurrence, and as an adjunct for *H. pylori* eradication.

The development of other P-CABs has since been discontinued, and of these discontinued compounds only the clinical trial results for linaprazan have been published (Kahrilas et al., 2007; Dent et al., 2008). Linaprazan provided similar efficacy to esomeprazole, but raised liver transaminase in a dose-dependent fashion. The clinical development of linaprazan was discontinued since it did not provide clinical benefit over esomeprazole in patient management (Maradey-Romero & Fass, 2014).

RQ-4, made by RaQualia Pharma, is currently in clinical development in Korea. The chemical structure of RQ-4 has not been published.

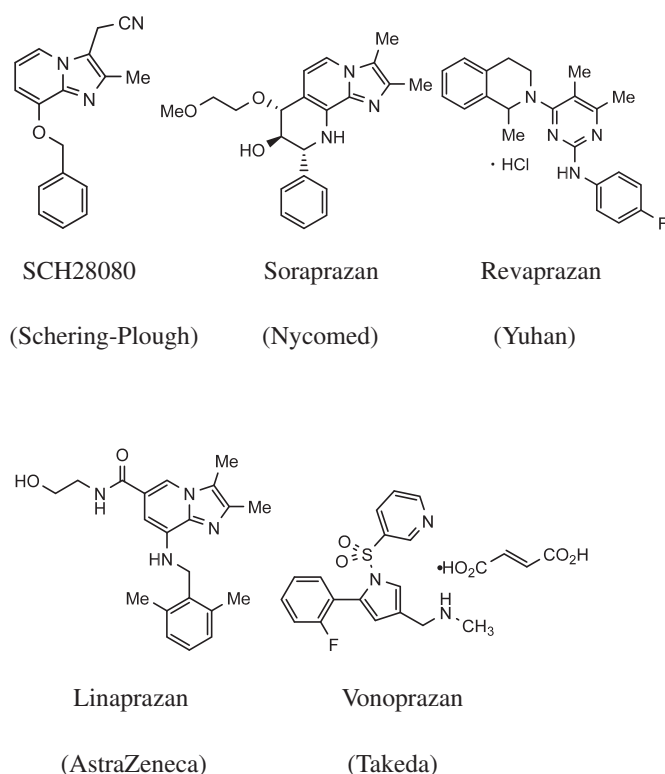


Fig. 2. Chemical structures of potassium-competitive acid blockers.

5.2. Mechanisms of action of potassium-competitive acid blockers

P-CABs are weak bases, and SCH28080, linaprazan and vonoprazan have pKa values of 5.6, 6.1, and 9.3, respectively (Keeling et al., 1988; Gedda et al., 2007; Hori et al., 2010). Linaprazan inhibited K^+ -stimulated H^+, K^+ -ATPase with an IC_{50} of 1.0 μM at pH 7.4, but was 8 times more potent at pH 6.4. The theoretical percent of protonated linaprazan is about 33% at pH 6.4 and less than 5% at pH 7.4. The inhibitory effect of SCH28080 is also weaker in neutral conditions (IC_{50} = 0.14 μM at pH 6.5 vs. IC_{50} = 2.5 μM at pH 7.4). These results suggest that protonated forms of P-CABs inhibit H^+, K^+ -ATPase. Linaprazan inhibited more potently in ion-tight vesicles than in ion-leaky vesicles, suggesting this agent concentrates in regions of low pH and has a luminal site of action (Gedda et al., 2007). As the pKa value of vonoprazan is 9.3, most of this compound should be protonated instantly and exert potent inhibition (IC_{50} = 19 nM at pH 6.5, IC_{50} = 28 nM at pH 7.5; Hori et al., 2010). Because protonated compounds are less membrane permeable than non-ionic compounds, protonated P-CABs are thought to concentrate in the acidic secretory canaliculi of parietal cells where they produce H^+, K^+ -ATPase inhibition. In rats administered vonoprazan, the stomach concentration of vonoprazan was much higher than the plasma concentration following oral administration of [^{14}C]vonoprazan (Hori et al., 2011), and following intravenous administration [3H]vonoprazan selectively accumulated in acid-secreting gastric parietal cells in the mucosa of the rat stomach (Matsukawa et al., 2016). In Heidenhain pouch dogs, the concentration of linaprazan in gastric juice exceeded the plasma concentration at 2 h after administration, and while the concentration of linaprazan was detectable in gastric juice 24 h after administration, it was undetectable in plasma in most animals (Holstein et al., 2004a, 2004b). These findings indicate that after entering into acidic secretory canaliculi, P-CABs are instantly protonated and accumulate at much higher concentrations than PPIs, and inhibit acid secretion by binding with H^+, K^+ -ATPase ionically and by competing with K^+ (Matsukawa et al., 2011). Scott et al. (2015) recently demonstrated that [^{14}C]vonoprazan binds equally to resting and

stimulated rabbit gastric glands, while autoradiographic analysis showed no difference in labeling between resting and stimulated gastric parietal cells, indicating that vonoprazan binds selectively to the parietal cell independent of acid secretion and vonoprazan labels both active and inactive H^+, K^+ -ATPase. This is in sharp contrast to the results obtained for omeprazole, where binding of omeprazole to parietal cells in rabbit gastric glands increased when acid secretion was stimulated and decreased with inhibition of secretion (Scott et al., 1993). Accumulation and acid activation are required for the action of PPIs, but are not required for the action of vonoprazan.

P-CABs bind selectively to the E_2-P form of H^+, K^+ -ATPase, a mechanism supported by the finding that SCH28080 binding affinity increased approximately 10-fold in the presence of ATP (Keeling et al., 1989; Mendlein & Sachs, 1990). SCH28080 inhibits K^+ -stimulated ATPase activity by competing with K^+ for binding to E_2-P and blocking K^+ -stimulated dephosphorylation. The binding sites of SCH28080 and vonoprazan have been investigated thoroughly using a H^+, K^+ -ATPase homology model based on the crystallographic structure of Na^+, K^+ -ATPase (Shin et al., 2011; Scott et al., 2015). Vonoprazan gains access to its binding site from the lumen through a wide entry space bounded by the TM1/TM2 and TM5/TM6 loops and the extracytoplasmic ends of TM4, TM8, and TM9. Following entry, this space closes and vonoprazan is trapped in the vestibule (Fig. 3). The positively charged N-methylamino side chain on vonoprazan is located within 2.4 Å of Glu795, producing strong hydrogen bonding and charge interaction with the K^+ site at Glu795, which is in contrast with the binding characteristics of SCH28080 and other P-CABs. Another divergence from the predicted binding of vonoprazan to the vestibule in H^+, K^+ -ATPase is the suggested hydrogen bonding between Tyr799 and the sulfone of vonoprazan (Shin et al., 2011). Improved binding site models have recently suggested that vonoprazan is largely occluded by H^+, K^+ -ATPase after binding, and predict that vonoprazan is buried in a greater surface area and occupies a larger percentage of its surface area than SCH28080. Vonoprazan exit into the lumen is hindered by asp137 and asn138 in the loop between TM1 and TM2, which presents an electrostatic barrier

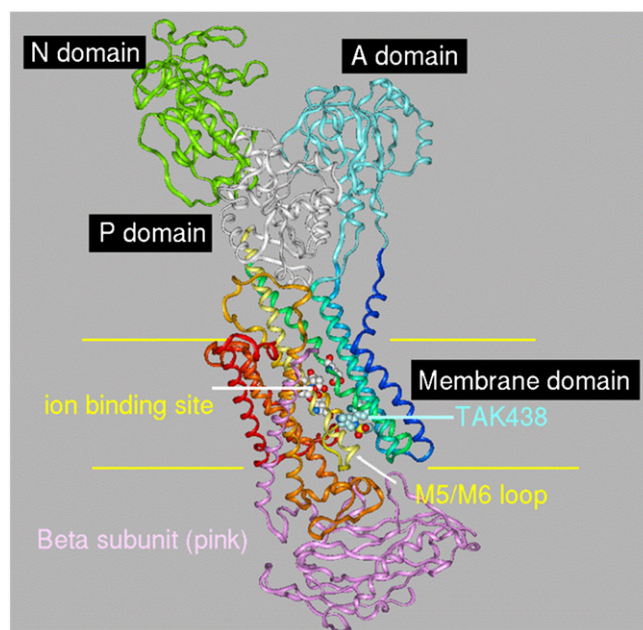


Fig. 3. Ribbon representation of H^+, K^+ -ATPase and the vonoprazan binding site (TAK-438). The membrane position is indicated with yellow lines. TM1, dark blue; TM2, cyan; TM3, light green; TM4, green-blue; TM5, light yellow; TM6, dark yellow; TM7, light brown; TM8, dark brown; TM9, light red; TM10, dark red. The position of the potassium ion binding site is close to the middle of the membrane (ball and stick), and vonoprazan (TAK-438; space filling in light blue) binds ~10 Å from the ion binding site in a cavity bounded by M1, TM2, TM4, and the TM5-TM6 loop. Reproduced from Shin et al. (2011) with permission from J Pharmacol Exp Ther.

to the movement of the sulfonyl group of vonoprazan (Scott et al., 2015). These binding characteristics could explain the very slow dissociation of vonoprazan from H^+ , K^+ -ATPase, and its more effective and longer action compared to other P-CABs.

5.3. Pharmacokinetics of potassium-competitive acid blockers

In studies conducted in healthy subjects in Japan and the UK, vonoprazan at 1 to 120 mg in Japan and 10 to 40 mg in the UK resulted in rapid peak plasma concentration (median T_{max} of up to 2 h), and an estimated half-life ($T_{1/2}$) of up to 9 h (Sakurai et al., 2015b). In repeated administration studies in Japanese and non-Japanese subjects, the median T_{max} of vonoprazan at 10 to 40 mg under fasting conditions was 1.5 h, with $T_{1/2}$ ranging from 5.7 to 8.8 h (Jenkins et al., 2015). The mean accumulation index was 1.1 to 1.2 in both studies, with only minor vonoprazan accumulation during repeated dosing. Pharmacokinetic parameters for each dose were similar on Day 1 and 7. Values of C_{max} and $AUC_{0-48\text{ h}}$ following administration of a single vonoprazan 20 mg were almost the same under fasting and fed conditions, showing that bioavailability was not affected by food intake. An exploratory analysis of Japanese data compared dose-normalized $AUC_{0-\tau}$ on Day 7 between different CYP2C19 genotypes and found no correlation between CYP2C19 genotype (*1/*1, *1/*2, *1/*3, *2/*2, *2/*3, *3/*3) and $AUC_{0-\tau}$. After oral administration of [^{14}C]vonoprazan in rats at 2 mg/kg, vonoprazan concentrations in plasma reached 17 ng/mL (C_{max}) at 0.3 h (T_{max}). Vonoprazan concentration in plasma decreased with a $T_{1/2}$ of 1.3 h and the $AUC_{0-24\text{ h}}$ of vonoprazan was 27 ng·h/mL. The bioavailability of vonoprazan after oral administration in rats was 10%. Oral administration of vonoprazan at 0.3 mg/kg in dogs indicated that T_{max} , C_{max} , $T_{1/2}$ and $AUC_{0-24\text{ h}}$ were 1.0 h, 30 ng/mL, 1.1 h, and 68 ng·h/mL, respectively. The bioavailability of vonoprazan after oral administration in dogs was 52% (Hori et al., 2011).

Repeated administration of revaprazan in healthy males resulted in peak plasma concentrations at 1.7 to 1.8 h after a single dose administered on Day 1 (100 to 200 mg), which declined with a $T_{1/2}$ of 2.2 to 2.4 h (Kim et al., 2010). The concentration-time profiles and pharmacokinetic characteristics of revaprazan following repeated administration (on Day 7) were similar to those observed after the first dose on Day 1. Another study of revaprazan administration to healthy volunteers showed linear pharmacokinetic characteristics and little accumulation after multiple administrations (Yu et al., 2004). Single oral doses of linaprazan (0.08 to 4.0 mg/kg) in healthy subjects also resulted in a rapid increase in plasma concentration, with a dose-proportional increase in AUC and C_{max} (Nilsson et al., 2005).

These findings indicate that P-CABs rapidly achieve peak plasma concentrations, partly because the compounds are acid-stable and can be administered as immediate-release formulations.

5.4. Pharmacodynamics of potassium-competitive acid blockers

The potent and long-lasting antisecretory effect of vonoprazan has been observed in both rats and dogs. Oral administration of vonoprazan at 4 mg/kg completely inhibited basal and 2-deoxy-D-glucose-stimulated gastric acid secretion in rats, and exhibited stronger inhibitory effect than lansoprazole. Vonoprazan increased the pH of gastric perfusate under histamine stimulation in rats to a higher value than lansoprazole or SCH28080, and this effect persisted for longer with vonoprazan than lansoprazole or SCH28080 (Hori et al., 2010). Vonoprazan also exhibited a more potent and longer-lasting inhibitory effect compared to lansoprazole in dogs (Hori et al., 2011). The significant antisecretory effect of vonoprazan in rats was not affected by cimetidine pretreatment; a result that is in contrast to lansoprazole, which failed to demonstrate an antisecretory effect after cimetidine pretreatment. This finding suggests the inhibitory effect of vonoprazan on gastric acid secretion is unaffected by gastric acid secretory state, while the inhibitory effect of PPIs

on gastric acid secretion is altered by gastric acid secretory state (De Graef & Woussen-Colle, 1986).

The pharmacodynamic effects of vonoprazan administered at 10 to 40 mg for 7 days were examined in Japanese and non-Japanese (UK) healthy subjects (Fig. 4; Jenkins et al., 2015). On day 1, there was a dose-dependent increase in mean intragastric pH, and the onset of this pH increase was rapid. At all dose levels, mean intragastric pH was >4.0 by 4 h after the first dose. The rapidity of onset was dose-dependent, with higher doses clearly having an earlier effect on pH compared to lower doses. The normal tendency for intragastric pH to fall during nighttime hours was also attenuated by vonoprazan in a strongly dose-dependent fashion. The mean intragastric pH-time profiles on Day 7 of repeated vonoprazan dosing showed that pH values before dosing and during the first 4 h after dosing were higher than at the corresponding time points on Day 1, and this increase in pH was strongly dose-dependent. The 24-h pH >4 and pH >5 holding time ratio (HTR) also increased dose-dependently and similarly in both studies (Table 1). Mean pH >4 and pH >5 HTRs after the 40 mg dose on Day 1 were 85.3% and 78.3% respectively (Japan) and 85.6% and 73.1% respectively (UK). Corresponding results for mean pH >4 and pH >5 HTRs on Day 7 were 100% and 98.6% respectively (Japan) and 93.2% and 85.0% respectively (UK). The acid-inhibitory effect of vonoprazan 20 mg administered daily for 7 days was compared with that of esomeprazole 20 mg or rabeprazole 10 mg in healthy Japanese subjects with the CYP2C19 extensive metabolizer genotype, and showed vonoprazan exhibited a significantly greater acid-inhibitory effect than esomeprazole and rabeprazole on both Day 1 and Day 7 (Fig. 5; Sakurai et al., 2015a). Kagami et al. (2016) also reported that mean pH >4 and pH >5 HTRs with single daily dosing of vonoprazan 20 mg were higher than those with esomeprazole 20 mg administered twice daily to a mixed CYP2C19 genotype group. The pharmacodynamic profile of vonoprazan therefore suggests that it might have advantages over existing acid-suppressing drugs that include maximum efficacy after the first dose, potency, prevention of nocturnal acid breakthrough (intragastric pH <4 for at least 60 continuous minutes during nighttime), reduction in nighttime gastric acidity, and the ability to dose at any time regardless of meals.

Pharmacodynamic studies of some other P-CABs have also been conducted at the developmental stage. Revaprazan administered at 100, 150 and 200 mg daily for 7 days increased pH >4 HTR in a dose-dependent manner in healthy volunteers. The mean pH >4 HTRs for revaprazan 200 mg in *H. pylori*-negative subjects were 28.1% at Day 1 and 34.2% at Day 7 (Kim et al., 2010), indicating revaprazan has a weaker acid suppressive effect than PPIs. After single doses of linaprazan (0.5 to 1.0 mg/kg) in healthy subjects, almost complete inhibition of acid production occurred within 1 h of dosing and continued for the duration of observation (15 h) at doses of 0.8 mg/kg and above (Nilsson et al., 2005). The pharmacodynamic data for vonoprazan, revaprazan and linaprazan suggest that the magnitude and duration of the inhibitory effect of P-CABs are mainly determined by dose, pKa, and plasma half-life.

5.5. Efficacy of potassium-competitive acid blockers compared with PPIs in patients with acid-related diseases

Phase 3 clinical studies of vonoprazan versus lansoprazole have been conducted in Japan to investigate the efficacy and safety of vonoprazan in the healing and maintenance of erosive esophagitis, prevention of aspirin- or NSAID-induced ulcer recurrence, gastric ulcer, duodenal ulcer, and *H. pylori* eradication. This section highlights clinical results for vonoprazan and lansoprazole in healing erosive esophagitis and *H. pylori* eradication to clarify the positioning of P-CABs in ARD management.

5.5.1. Healing of erosive esophagitis

In a phase 2 clinical study, vonoprazan or lansoprazole was administered to a total of 732 patients with erosive esophagitis. The results are

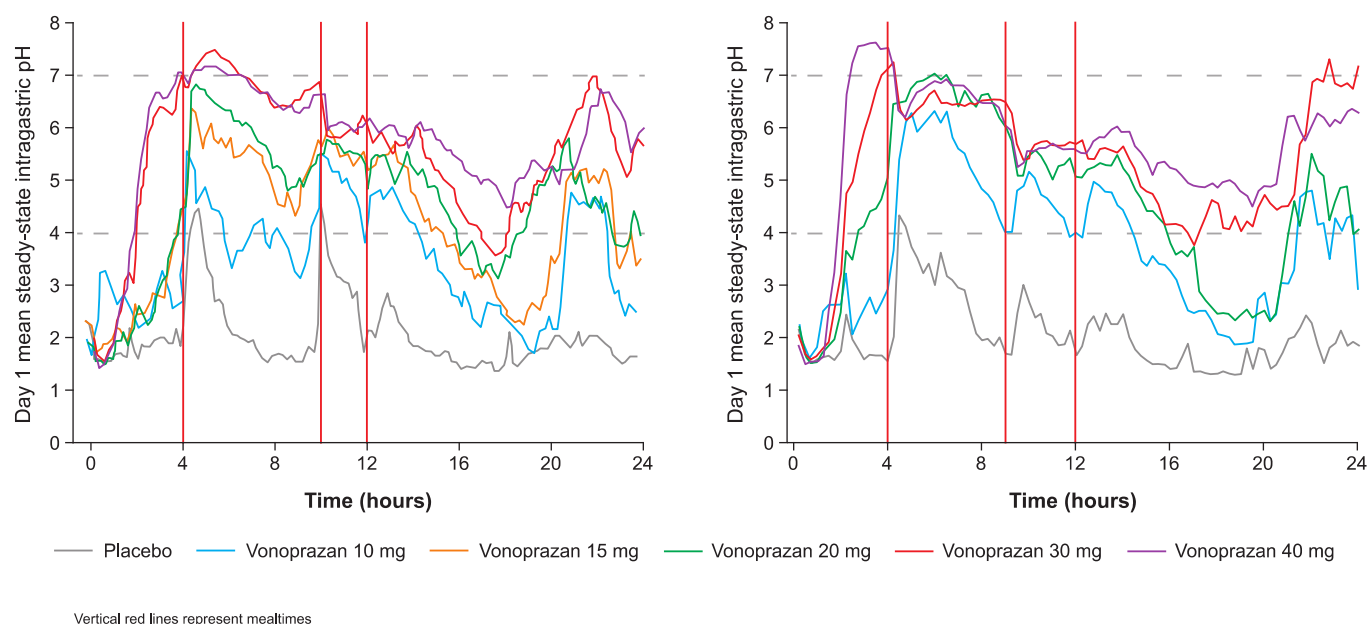


Fig. 4. Mean intragastric pH on Day 1 in healthy male subjects after administering vonoprazan (TAK-438) 10–40 mg after overnight fasting in Japanese (left panel) and UK (right panel) studies (Japan N = 60; UK N = 48). Reproduced from Jenkins et al. (2015) with permission from Alim Pharmacol Ther.

summarized in Table 2 below, and show every vonoprazan dose was non-inferior to lansoprazole 30 mg ($P < 0.004$) (Ashida et al., 2015). In a phase 3 clinical study, a total of 409 patients with LA grades A–D esophagitis were randomized to vonoprazan 20 mg or lansoprazole 30 mg once daily for 8 weeks, and healing of esophagitis was examined by endoscopy at 2, 4 and 8 weeks. The healing rate at 8 weeks, the primary endpoint of the study, was 99.0% in the vonoprazan group and 95.5% in the lansoprazole group. In post-hoc analyses, stratification according to LA grade of esophagitis at baseline revealed a significant difference in the healing rate between vonoprazan and lansoprazole for grade C/D patients; the healing rates at 8 weeks were 98.7% and 87.5%, respectively. The secondary endpoint was healing rate at 4 weeks, which was 96.6% in the vonoprazan group and 92.5% in the lansoprazole group. The healing rate for vonoprazan 20 mg at 4 weeks was almost identical to that for lansoprazole 30 mg at 8 weeks. The healing rate after 2 weeks treatment in the vonoprazan group (90.7%)

was also higher than that observed in the lansoprazole group (81.9%, $P < 0.0132$ [Fisher's exact test; Post-hoc analysis]; Ashida et al., 2016).

5.5.2. *Helicobacter pylori* eradication

To compare first line *H. pylori* eradication therapies, a total of 650 *H. pylori*-positive patients with cicatrized gastric or duodenal ulcers were randomized to triple therapy with either vonoprazan (vonoprazan 20 mg, amoxicillin 750 mg, clarithromycin 200 mg or 400 mg twice daily for 7 days) or to triple therapy with lansoprazole (lansoprazole 30 mg, amoxicillin 750 mg, clarithromycin 200 mg or 400 mg twice daily for 7 days). Fifty of 101 subjects in whom eradication with a first line therapy failed received a 7-day course of second line therapy (vonoprazan 20 mg, amoxicillin 750 mg, metronidazole 250 mg twice daily). The first line *H. pylori* eradication rate was 92.6% in the vonoprazan group and 75.9% in the lansoprazole group. Non-inferiority of vonoprazan to lansoprazole was verified. A post-hoc analysis subsequently indicated that vonoprazan performed significantly better than lansoprazole as a component in the first line therapy. Notably, the *H. pylori* eradication rate was significantly higher in the vonoprazan group compared with the lansoprazole group in the subjects with clarithromycin resistance (82.0% and 40.0%, respectively; pre-planned grouping and post-hoc statistical test). Second line therapy with vonoprazan resulted in eradication rate of 98% (Murakami et al., 2016).

Only one report on revaprazan efficacy could be found in the public domain. This report compared revaprazan with omeprazole for the healing of gastric ulcer in South Korean patients. Two hundred and ninety-two patients were randomized to 4 to 8 weeks of treatment with either revaprazan 200 mg or omeprazole 20 mg. ITT analysis revealed similar cumulative healing rates; 93.0% for revaprazan treatment and 89.6% for omeprazole treatment (Chang et al., 2007).

Comparative studies of linaprazan and esomeprazole have been conducted in the healing of erosive esophagitis and the treatment of patients with nonerosive reflux disease. Nonerosive reflux disease is defined as presentation of typical GERD symptoms such as heartburn or regurgitation in the absence of visible esophageal mucosal break, while erosive esophagitis is defined as an endoscopically-confirmed esophageal mucosal break. After 4 weeks of treatment, erosive esophagitis healing rates were 76.9%, 78.2%, 81.1% and 81.9% in linaprazan 25, 50, 75 mg and esomeprazole 40 mg treatment groups, respectively.

Table 1

Dose–response relationship for mean 24-h intragastric pH >4 and >5 holding time ratio [HTR (%) during 24-h dosing interval in healthy subjects who received vonoprazan 10–40 mg once daily at a fixed dose level for 7 consecutive days in Japanese and UK studies (reference: Jenkins et al., 2015).

	Placebo	Vonoprazan		
		10 mg	20 mg	40 mg
Japanese study				
n	15	9	9	9
24-h pH > 4 HTR (%)				
Day 1	8.3 ± 4.0	38.4 ± 22.3	63.3 ± 17.9	85.3 ± 8.3
Day 7	5.6 ± 3.5	63.3 ± 8.7	83.4 ± 16.7	100.0 ± 0.0
24-h pH > 5 HTR (%)				
Day 1	3.7 ± 2.4	25.1 ± 19.0	53.5 ± 21.5	78.3 ± 10.6
Day 7	1.5 ± 1.5	52.6 ± 10.7	73.2 ± 18.9	98.6 ± 2.0
UK study				
n	12	9	9	9
24-h pH > 4 HTR (%)				
Day 1	6.2 ± 3.2	43.1 ± 21.2	62.7 ± 16.8	85.6 ± 7.4
Day 7	6.5 ± 4.5	60.2 ± 19.1	85.2 ± 12.3	93.2 ± 10.5
24-h pH > 5 HTR (%)				
Day 1	2.6 ± 2.0	31.5 ± 20.8	49.2 ± 19.9	73.1 ± 11.0
Day 7	3.2 ± 3.2	49.5 ± 15.8	78.6 ± 14.0	85.0 ± 21.7

All data are represented as means ± S.D.

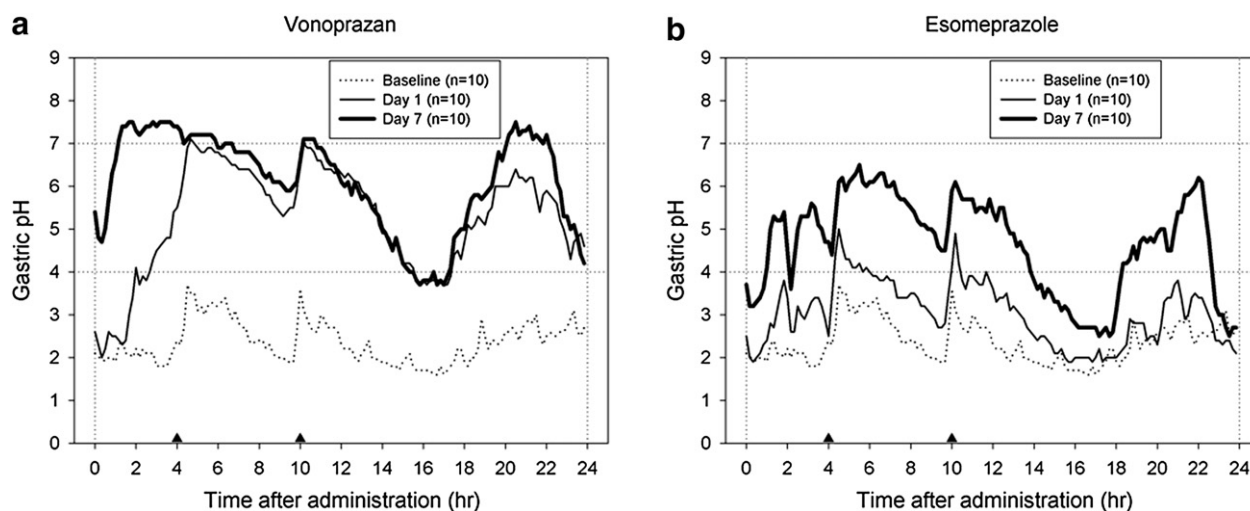


Fig. 5. Time courses of intragastric pH over 24 h for (a) vonoprazan 20 mg and (b) esomeprazole 20 mg on Days 1 and 7 ($n = 10$). The pH data from Day-2 to Day-1 were used as baseline data for both treatments. All study drugs were administered at time 0 (as a rule, 9:00 AM) on Days 1–7. The triangles indicate the timing of meals. Reproduced from Sakurai et al. (2015a) with permission from Alim Pharmacol Ther.

The healing rates at 2 and 8 weeks were also comparable among treatments (Kahrilas et al., 2007). No significant differences were observed between lansoprazole 25, 50, 75 mg and esomeprazole 20 mg in the treatment of patients with nonerosive reflux disease (Dent et al., 2008). Even though lansoprazole resulted in a faster onset of acid inhibition, it did not provide clinical benefit over esomeprazole in the management of patients with erosive esophagitis or nonerosive reflux disease, and its development was discontinued (Sachs et al., 2010; Hunt & Scarpignato, 2015).

5.6. Safety of potassium-competitive acid blockers

In a clinical phase 3 study of treatment of patients with erosive esophagitis in Japan, the incidences of treatment-emergent adverse events with vonoprazan 20 mg were similar to those with lansoprazole 30 mg; 22.2% in the vonoprazan group vs. 22.3% in the lansoprazole group (Ashida et al., 2016). In a study assessing 24-week maintenance treatment for healed erosive esophagitis, the overall incidence of treatment-emergent adverse events was comparable between the treatment groups; 54.0% in the vonoprazan 10 mg group, 58.8% in the vonoprazan 20 mg group, and 51.2% in the lansoprazole 15 mg group (Umegaki et al., 2014). Importantly, vonoprazan did not increase serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin levels, probably because its chemical structure differs significantly from other P-CABs such as lansoprazole. Greater increases in serum gastrin and pepsinogen I and II were observed during treatment with vonoprazan than with lansoprazole, probably as a consequence of greater inhibition of gastric acid secretion by vonoprazan compared with lansoprazole (Ashida et al., 2015).

In a clinical study of lansoprazole (25, 50 and 75 mg) and esomeprazole 20 mg for the treatment of nonerosive reflux disease, the incidence of adverse events was similar across treatment groups, and headache was the only adverse event that occurred in more than 5% of patients in any group

(Dent et al., 2008). In the lansoprazole treatment groups, increases in liver transaminases were observed more commonly at higher doses, and for the most part these increases developed after 4 weeks of treatment. SCH28080 shares the imidazopyridine ring structure of lansoprazole and has been shown to affect the liver (Parsons & Keeling, 2005). AR-H047108, an imidazopyridine-related compound of lansoprazole, is reported to cause hepatotoxicity in dogs (Berg et al., 2008). These results suggest a possible chemical class effect of imidazopyridine compounds that causes liver toxicity.

6. Summary

During the past 40 years, treatment of PUD has changed dramatically from diet and surgery to H₂RAs, which were followed by PPIs. H₂RAs were the first effective pharmacological treatment of PUD, but their relatively weak efficacy for GERD and the development of patient tolerance required the development of more effective acid suppressants. Since the introduction of PPIs, outcomes in ARD therapy have improved dramatically, and now PPIs are the first choice of treatment of ARDs. However, there are still areas of medical need in acid control that are not met by PPIs, because 1) PPIs produce insufficient gastric acid suppression, especially at night, 2) PPIs are slow to achieve steady state inhibition of gastric acid secretion, typically taking 3 to 5 days to achieve maximum inhibition of acid secretion, 3) there are large interindividual variations in efficacy due to CYP2C19 metabolism, and 4) mealtime dosing is required to ensure adequate levels of the drug during periods of H⁺,K⁺-ATPase activation.

The discovery of *H. pylori* and its causative role in PUD, gastritis and gastric cancer made its eradication the standard of care for patients with *H. pylori*. The recent increasing prevalence of antibiotic resistance and decrease in eradication rates provided by the regimens that include PPIs necessitates the development of more potent gastric acid suppressants. P-CABs have several advantages over PPIs that are translated into

Table 2

Proportion of healed erosive esophagitis subjects as shown by endoscopy at week 4 (reference: Ashida et al., 2015).

LA grade	Lansoprazole 30 mg	Vonoprazan			
		5 mg	10 mg	20 mg	40 mg
Overall	123/132 (93.2)	132/143 (92.3)	123/133 (92.5)	136/144 (94.4)	130/134 (97.0)
A/B	83/86 (96.5)	84/88 (95.5)	85/89 (95.5)	86/94 (91.5)	82/84 (97.6)
C/D	40/46 (87.0)	48/55 (87.3)	38/44 (86.4)	50/50 (100)	48/50 (96.0)

Data are represented as numbers of subjects with percentages in parentheses.

clinical benefits in the treatment of erosive esophagitis and *H. pylori* eradication: 1) P-CABs rapidly achieve therapeutic plasma levels and provide almost complete inhibition of gastric acid secretion from the first dose; 2) there is much less interindividual variation in P-CAB metabolism and efficacy due to no or minimal involvement of CYP2C19 metabolism; 3) P-CABs action is independent of secretory state; 4) P-CABs are acid stable and do not require an enteric coating formulation. Since the development of SCH28080, many pharmaceutical companies have attempted to develop P-CABs. Revaprazan is only used in South Korea and India, and has not been developed for clinical use in other countries. The clinical development of other compounds, such as soraprazan, CS526 and linaprazan, has been discontinued probably because these agents could not demonstrate effectiveness superior to PPIs and produced signs of hepatic toxicity.

Vonoprazan, recently approved in Japan, has a different chemical structure and a higher pKa value compared to other P-CABs, and has produced effective and longer-lasting acid suppression in both animals and humans. In clinical studies in Japan, post-hoc analyses indicated that vonoprazan was more effective than lansoprazole in the healing of reflux esophagitis and *H. pylori* eradication. Vonoprazan has also been shown to be safe and well tolerated in clinical studies, with an incidence of adverse events similar to that of lansoprazole. Because of their enhanced effectiveness and good tolerability, it is likely that P-CABs, such as vonoprazan, will further improve the treatment of ARD.

Conflict of interest statement

The authors are employees of Takeda.

The present manuscript has not been published and is not under consideration for publication elsewhere.

References

- Abelö, A., Andersson, T. B., Antonsson, M., Naudot, A. K., Skånberg, I., & Weidolf, L. (2000). Stereoselective metabolism of omeprazole by human cytochrome P450 enzymes. *Drug Metab Dispos* 28, 966–972.
- Andersson, K., & Carlsson, E. (2005). Potassium-competitive acid blockade: a new therapeutic strategy in acid-related diseases. *Pharmacol Ther* 108, 294–307.
- Andersson, T., Hassan-Alin, M., Hasselgren, G., Röhs, K., & Weidolf, L. (2001). Pharmacokinetic studies with esomeprazole, the (S)-isomer of omeprazole. *Clin Pharmacokinet* 40, 411–426.
- Asano, S., Kawada, K., Kimura, T., Grishin, A. V., Caplan, M. J., & Takeguchi, N. (2000). The roles of carbohydrate chains of the β -subunit on the functional expression of gastric H^+ , K^+ -ATPase. *J Biol Chem* 275, 8324–8330.
- Ash, A. S. F., & Schild, H. O. (1966). Receptors mediating some actions of histamine. *Br J Pharmacol Chemother* 27, 427–439.
- Ashida, K., Sakurai, Y., Nishimura, A., Kudou, K., Hiramatsu, N., Umegaki, E., et al. (2015). Randomised clinical trial: a dose-ranging study of vonoprazan, a novel potassium-competitive acid blocker, vs. lansoprazole for the treatment of erosive oesophagitis. *Aliment Pharmacol Ther* 42, 685–695.
- Ashida, K., Sakurai, Y., Hori, T., Nishimura, A., Hiramatsu, N., Umegaki, E., & Iwakiri, K. (2016). Randomised clinical trial: vonoprazan, a novel potassium-competitive acid blocker, vs. lansoprazole for the healing of erosive oesophagitis. *Aliment Pharmacol Ther* 43, 240–251.
- Beil, W., Hackbarth, I., & Sewing, K. F. (1986). Mechanism of gastric antisecretory effect of SCH28080. *Br J Pharmacol* 88, 19–23.
- Beisvag, V., Falck, G., Loennechen, J. P., Qvigstad, G., Jynge, P., Skomedal, T., Osnes, J. B., et al. (2003). Identification and regulation of the gastric H^+ , K^+ -ATPase in the rat heart. *Acta Physiol Scand* 179, 251–262.
- Bell, N. J., Burget, D., Howden, C. W., Wilkinson, J., & Hunt, R. H. (1992). Appropriate acid suppression for the management of gastro-oesophageal reflux disease. *Digestion* 51 (Suppl. 1), 59–67.
- Berg, A. L., Böttcher, G., Andersson, K., Carlsson, E., Lindström, A. K., Huby, R., et al. (2008). Early stellate cell activation and veno-occlusive-disease (VOD)-like hepatotoxicity in dogs treated with AR-H047108, an imidazopyridine proton pump inhibitor. *Toxicol Pathol* 36, 727–737.
- Besancon, M., Shin, J. M., Mercier, F., Munson, K., Miller, M., Hersey, S., & Sachs, G. (1993). Membrane topology and omeprazole labeling of the gastric H^+ , K^+ -adenosinetriphosphatase. *Biochemistry* 32, 2345–2355.
- Bhatt, D. L., Cryer, B. L., Contant, C. F., Cohen, M., Lanas, A., Schnitzer, T. J., et al. (2010). Clopidogrel with or without omeprazole in coronary artery disease. *N Engl J Med* 363, 1909–1917.
- Black, J. W., Duncan, W. A. M., Durant, C. J., Ganellin, C. R., & Parsons, E. M. (1972). Definition and antagonism of histamine H_2 -receptors. *Nature* 236, 385–390.
- Boyce, M., David, O., Darwin, K., Mitchell, T., Johnston, A., & Warrington, S. (2012). Single oral doses of netazepide (YF476), a gastrin receptor antagonist, cause dose-dependent, sustained increases in gastric pH compared with placebo and ranitidine in healthy subjects. *Aliment Pharmacol Ther* 36, 181–189.
- Brimblecombe, R. W., Duncan, W. A., Durant, G. J., Ganellin, C. R., Parsons, M. E., & Black, J. W. (1975). The pharmacology of cimetidine, a new histamine H_2 -receptor antagonist. *Br J Pharmacol* 53, 435P–436P.
- Burget, D. W., Chiverton, S. G., & Hunt, R. H. (1990). Is there an optimal degree of acid suppression for healing of duodenal ulcers? A model of the relationship between ulcer healing and acid suppression. *Gastroenterology* 99, 345–351.
- Chang, R., Chung, I. S., Park, S. H., Kim, S. K., Choi, S. R., Song, G. A., et al. (2007). Phase III clinical trial of revaprazan (revanex R) for gastric ulcer. *Korean J Gastrointest Endosc* 34, 312–319.
- Chey, W. D., Mody, R. R., & Izat, E. (2010). Patient and physician satisfaction with proton pump inhibitors (PPIs): are there opportunities for improvement? *Dig Dis Sci* 55, 3415–3422.
- Chiu, P. J., Casciano, C., Tetzloff, G., Long, J. F., & Barnett, A. (1983). Studies on the mechanisms of the antisecretory and cytoprotective actions of SCH28080. *J Pharmacol Exp Ther* 226, 121–125.
- De Graef, J., & Woussen-Colle, M. C. (1986). Influence of the stimulation state of the parietal cells on the inhibitory effect of omeprazole on gastric acid secretion in dogs. *Gastroenterology* 91, 333–337.
- Dent, J., Kahrilas, P. J., Hatlebakk, J., Vakil, N., Denison, H., Franzén, S., & Lundborg, P. (2008). A randomized, comparative trial of a potassium-competitive acid blocker (AZD0865) and esomeprazole for the treatment of patients with nonerosive reflux disease. *Am J Gastroenterol* 103, 20–26.
- Dufresne, M., Seva, C., & Fourmy, D. (2006). Cholecystokinin and gastrin receptors. *Physiol Rev* 86, 805–847.
- Emerson, C. R., & Marzella, N. (2010). Dexlansoprazole: a proton pump inhibitor with a dual delayed-release system. *Clin Ther* 32, 1578–1596.
- Ene, M. D., Khan-Daneshmend, T., & Roberts, C. J. C. (1982). A study of the inhibitory effects of SCH 28080 on gastric secretion in man. *Br J Pharmacol* 76, 389–391.
- Fellenius, E., Berglindh, T., Sachs, G., Olbe, L., Elander, B., Sjöstrand, S. E., & Wallmark, B. (1981). Substituted benzimidazoles inhibit gastric acid secretion by blocking (H^+ + K^+)-ATPase. *Nature* 290, 159–161.
- Feurle, G. E. (1975). Effect of rising intragastric pH induced by several antacids on serum gastrin concentrations in duodenal ulcer patients and in a control group. *Gastroenterology* 68, 1–7.
- Fiorucci, S., Clausi, G. G., Farinelli, M., Santucci, L., Farroni, F., Pelli, M. A., & Morelli, A. (1988). Do anticholinergics interact with histamine H_2 receptor antagonists on night intragastric acidity in active duodenal ulcer patients? *Am J Gastroenterol* 83, 1371–1375.
- Forté, J. G., & Zhu, L. (2010). Apical recycling of the gastric parietal cell H,K -ATPase. *Annu Rev Physiol* 72, 273–296.
- Forté, T. M., Machen, T. E., & Forté, J. G. (1977). Ultrastructural changes in oxyntic cells associate with secretory function: a membrane-recycling hypothesis. *Gastroenterology* 73, 941–955.
- Frelinger, A. L., III, Lee, R. D., Mulford, D. J., Wu, J., Nudurupati, S., Nigam, A., et al. (2012). A randomized, 2-period, crossover design study to assess the effects of dexlansoprazole, lansoprazole, esomeprazole, and omeprazole on the steady-state pharmacokinetics and pharmacodynamics of clopidogrel in healthy volunteers. *J Am Coll Cardiol* 59, 1304–1311 [Erratum in J Am Coll Cardiol (2012) 60, 566–567].
- Furuta, T., Shirai, N., Sugimoto, M., Nakamura, A., Hishida, A., & Ishizaki, T. (2005). Influence of CYP2C19 pharmacogenetic polymorphism on proton pump inhibitor-based therapies. *Drug Metab Pharmacokinet* 20, 153–167.
- Ganser, A. L., & Forté, J. G. (1973). K^+ -stimulated ATPase in purified microsomes of bullfrog oxyntic cells. *Biochim Biophys Acta* 307, 169–180.
- Gedda, K., Briving, C., Svensson, K., Maxväll, I., & Andersson, K. (2007). Mechanism of action of AZD0865, a K^+ -competitive inhibitor of gastric H^+ , K^+ -ATPase. *Biochem Pharmacol* 73, 198–205.
- Geibel, J., Abraham, R., Modlin, I., & Sachs, G. (1995). Gastrin-stimulated changes in Ca^{2+} concentration in parietal cells depends on adenosine 3',5'-cyclic monophosphate levels. *Gastroenterology* 109, 1060–1067.
- Hall, K., Perez, G., Anderson, D., Gutierrez, C., Munson, K., Hersey, S. J., et al. (1990). Location of the carbohydrates present in the H,K -ATPase vesicles isolated from hog gastric mucosa. *Biochemistry* 29, 701–706.
- Hatlebakk, J. G., & Berstad, A. (1996). Pharmacokinetic optimization in the treatment of gastro-oesophageal reflux disease. *Clin Pharmacokinet* 31, 386–406.
- Helander, H. F., & Hirschowitz, B. I. (1972). Quantitative ultrastructural studies on gastric parietal cells. *Gastroenterology* 63, 951–961.
- Helander, H. F., Ramsay, C. H., & Regårdh, C. G. (1985). Localization of omeprazole and metabolites in the mouse. *Scand J Gastroenterol* 20 (Suppl. 108), 95–104.
- Herrmann, M., Selige, J., Raffael, S., Sachs, G., Brambilla, A., & Klein, T. (2007). Systematic expression profiling of the gastric H^+ , K^+ -ATPase in human tissue. *Scand J Gastroenterol* 42, 1275–1288.
- Hinkle, K. L., Bane, G. C., Jazayeri, A., & Samuelson, L. C. (2003). Enhanced calcium signaling and acid secretion in parietal cells isolated from gastrin-deficient mice. *Am J Physiol Gastrointest Liver Physiol* 284, G145–G153.
- Holstein, B., Holmberg, A., Florentzson, M., Aurell Holmberg, A., Andersson, M., & Andersson, K. (2004a). AZD0865, a potassium-competitive acid blocker (P-CAB), provides predictable inhibition of acid secretion with repeated dosing in the dog. *Eur J Pharm Sci* 23 (Suppl. 1), S8.
- Holstein, B., Holmberg, A., Florentzson, M., Aurell Holmberg, A., Andersson, M., & Andersson, K. (2004b). AZD0865 – a new potassium-competitive acid blocker – exhibits maximal gastric antisecretory effects from first dose. *Gastroenterology* 126, A-334 M1437.
- Hori, Y., Imanishi, A., Matsukawa, J., Tsukimi, Y., Nishida, H., Anikawa, Y., ... Inatomi, N. (2010). 1-[5-(2-Fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1H-pyrrol-3-yl]-N-methylmethanamine

- monofumarate (TAK-438), a novel and potent potassium-competitive acid blocker for the treatment of acid-related diseases. *J Pharmacol Exp Ther* 335, 231–238.
- Hori, Y., Matsukawa, J., Takeuchi, T., Nishida, H., Kajino, M., & Inatomi, N. (2011). A study comparing the antisecretory effect of TAK-438, a novel potassium-competitive acid blocker, with lansoprazole in animals. *J Pharmacol Exp Ther* 337, 797–804.
- Howden, C. W., Burget, D. W., & Hunt, R. H. (1991). A meta-analysis to predict gastric ulcer healing from acid suppression. *Gastroenterology* 100, A3.
- Howden, C. W., Burget, D. W., & Hunt, R. H. (1994). Appropriate acid suppression for optimal healing of duodenal ulcer and gastro-oesophageal reflux disease. *Scand J Gastroenterol Suppl* 201, 79–82.
- Hunt, R. H. (1999). Importance of pH control in the management of GERD. *Arch Intern Med* 159, 649–657.
- Hunt, R. H., & Scarpignato, C. (2015). Potassium-competitive acid blockers (P-CABs): are they finally ready for prime time in acid-related diseases? *Clin Transl Gastroenterol* 6, e119.
- Hunt, R. H., Armstrong, D., Yaghoobi, M., James, C., Chen, Y., Leonard, J., et al. (2008). Predictable prolonged suppression of gastric acidity with a novel proton pump inhibitor, AGN201904-Z. *Aliment Pharmacol Ther* 28, 187–199.
- Jenkins, H., Sakurai, Y., Nishimura, A., Okamoto, H., Hibberd, M., Jenkins, R., et al. (2015). Randomised clinical trial: safety, tolerability, pharmacokinetics and pharmacodynamics of repeated doses of TAK-438 (vonoprazan), a novel potassium-competitive acid blocker, in healthy male subjects. *Aliment Pharmacol Ther* 41, 636–648.
- Kagami, T., Sahara, S., Ichikawa, H., Uotani, T., Yamade, M., Sugimoto, M., et al. (2016). Potent acid inhibition by vonoprazan in comparison with esomeprazole, with reference to CYP2C19 genotype. *Aliment Pharmacol Ther* 43, 1048–1059.
- Kahrilas, P. J., Dent, J., Lauritsen, K., Malfertheiner, P., Denison, H., Franzén, S., & Hasselgren, G. (2007). A randomized, comparative study of three doses of AZD0865 and esomeprazole for healing of reflux esophagitis. *Clin Gastroenterol Hepatol* 5, 1385–1391.
- Kanai, Y., Nohara, A., Honda, H., Kanno, M., & Sanno, Y. (1969) inventors, Takeda Chemical Ind. Ltd., assignee. Process for producing thioamide derivatives. *Japanese patent application*, 1969 July (Japanese Patent Notification 1972: 47-41902).
- Kanno, M., Narumi, S., Hirata, T., Gomaibashi, K., Kanai, Y., Nohara, A., & Sanno, Y. (1973). Inhibition of the gastric secretion in the rat by thioacetamide derivatives. *J Takeda Res Lab* 32, 181–187.
- Keeling, D. J., Laing, S. M., & Senn-Bilfinger, J. (1988). SCH28080 is a lumenally acting, K⁺-site inhibitor of the gastric (H⁺+K⁺)-ATPase. *Biochem Pharmacol* 37, 2231–2236.
- Keeling, D. J., Malcolm, R. C., Laing, S. M., Ife, R. J., & Leach, C. A. (1991). SK&F 96067 is a reversible, lumenally acting inhibitor of the gastric (H⁺+K⁺)-ATPase. *Biochem Pharmacol* 42, 123–130.
- Keeling, D. J., Taylor, A. G., & Schudt, C. (1989). The binding of a K⁺ competitive ligand, 2-methyl-8-(phenylmethoxy)imidazo[1,2-a]pyridine 3-acetonitrile, to the gastric (H⁺+K⁺)-ATPase. *J Biol Chem* 264, 5545–5551.
- Kim, H. K., Park, S. H., Cheung, D. Y., Cho, Y. S., Kim, J. I., Kim, S. S., et al. (2010). Clinical trial: inhibitory effects of revaprazan on gastric acid secretion in healthy male subjects. *J Gastroenterol Hepatol* 25, 1618–1625.
- Kleinman, L., McIntosh, E., Ryan, M., Schmier, J., Crawley, J., Lock, R. G., et al. (2002). Willingness to pay for complete symptom relief of gastroesophageal reflux disease. *Arch Intern Med* 162, 1361–1366.
- Kraut, J. A., Helander, K. G., Helander, H. F., Iroezzi, N. D., Marcus, E. A., & Sachs, G. (2001). Detection and localization of H⁺-K⁺-ATPase isoforms in human kidney. *Am J Physiol Renal Physiol* 281, F763–F768.
- Kubo, K., Oda, K., Kaneko, T., Satoh, H., & Nohara, A. (1990). Synthesis of 2-[(4-fluoroalkoxy-2-pyridyl)methylsulfenyl]-1H-benzimidazoles as antiulcer agents. *Chem Pharm Bull* 38, 2853–2858.
- Kukulka, M., Eisenberg, C., & Nadurupati, S. (2011). Comparator pH study to evaluate the single-dose pharmacodynamics of dual delayed-release dexlansoprazole 60 mg and delayed-release esomeprazole 40 mg. *Clin Exp Gastroenterol* 4, 213–220.
- Kuo, C. H., Lu, C. Y., Shih, H. Y., Liu, C. J., Wu, M. C., Hu, H. M., et al. (2014). CYP2C19 polymorphism influences *Helicobacter pylori* eradication. *World J Gastroenterol* 20, 16029–16036.
- Lambrecht, N. W. G., Yakubov, I., Scott, D., & Sachs, G. (2005). Identification of the K efflux channel coupled to the gastric H-K-ATPase during acid secretion. *Physiol Genomics* 21, 81–91.
- Lee, R. D., Mulford, D., Wu, J., & Atkinson, S. N. (2010). The effect of time-of-day dosing on the pharmacokinetics and pharmacodynamics of dexlansoprazole MR: evidence for dosing flexibility with a dual delayed release proton pump inhibitor. *Aliment Pharmacol Ther* 31, 1001–1011.
- Lindberg, P., Nordberg, P., Alminger, T., Brändström, A., & Wallmark, B. (1986). The mechanism of action of the gastric acid secretion inhibitor omeprazole. *J Med Chem* 29, 1327–1329.
- Lundell, L. (2015). The physiological background behind and course of development of the first proton pump inhibitor. *Scand J Gastroenterol* 50, 680–684.
- Maeda, M., Ishizaki, J., & Futai, M. (1988). cDNA cloning and sequence determination of pig gastric (H⁺+K⁺)-ATPase. *Biochem Biophys Res Commun* 157, 203–209.
- Malen, C. E., & Danree, B. H. (1971). New thiocarboxamides derivatives with specific gastric antisecretory properties. *J Med Chem* 14, 244–246.
- Malfertheiner, P., Link, A., & Selgrad, M. (2014). *Helicobacter pylori*: perspectives and time trends. *Nat Rev Gastroenterol Hepatol* 11, 628–638.
- Maradey-Romero, C., & Fass, R. (2014). New and future drug development for gastroesophageal reflux disease. *J Neurogastroenterol Motil* 20, 6–16.
- Marshall, B. J., & Warren, J. R. (1984). Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet* 1, 1311–1315.
- Matsukawa, J., Hori, Y., Nishida, H., Kajino, M., & Inatomi, N. (2011). A comparative study on the modes of action of TAK-438, a novel potassium-competitive acid blocker, and lansoprazole in primary cultured rabbit gastric glands. *Biochem Pharmacol* 81, 1145–1151.
- Matsukawa, J., Kogame, A., Tagawa, Y., & Inatomi, N. (2016). Radiographic localization study of a novel potassium-competitive acid blocker, vonoprazan, in the rat gastric mucosa. *Dig Dis Sci* 61, 1888–1894.
- McCabe, R. D., & Young, D. B. (1992). Evidence of a K(+)-(H+)-ATPase in vascular smooth muscle cells. *Am J Physiol Heart Circ Physiol* 262, H1955–H1958.
- Mejia, A., & Kraft, W. K. (2009). Acid peptic diseases: pharmacological approach to treatment. *Expert Rev Clin Pharmacol* 2, 295–314.
- Mendlein, J., & Sachs, G. (1990). Interaction of a K⁺-competitive inhibitor, a substituted imidazo[1,2-a]pyridine, with the phospho- and dephosphoenzyme forms of H⁺,K⁺-ATPase. *J Biol Chem* 265, 5030–5036.
- Murakami, K., Sakurai, Y., Shiino, M., Funao, N., Nishimura, A., & Asaka, M. (2016). Vonoprazan, a novel potassium-competitive acid blocker, as a component of first-line and second-line therapy for *Helicobacter pylori* eradication: a phase III, randomized, double-blind study. *Gut* 65, 1439–1446.
- Nagaya, H., Inatomi, N., Nohara, A., & Satoh, H. (1991). Effects of enantiomers of lansoprazole (AG-1749) on (H⁺+K⁺)-ATPase activity in canine gastric microsomes and acid formation in isolated canine parietal cells. *Biochem Pharmacol* 42, 1875–1878.
- Nagaya, H., Satoh, H., Kubo, K., & Maki, Y. (1989). Possible mechanism for the inhibition of gastric (H⁺+K⁺)-adenosine triphosphatase by the proton pump inhibitor AG-1749. *J Pharmacol Exp Ther* 248, 799–805.
- Nguyen, N., Kozar-Gorevich, N., Gliddon, B. L., Smolka, A. J., Clayton, A. H., Gleeson, P. A., & van Driel, I. R. (2013). Independent trafficking of the KCNQ1 K⁺ channel and H⁺-K⁺-ATPase in gastric parietal cells from mice. *Am J Physiol Gastrointest Liver Physiol* 304, G157–G166.
- Nilsson, C., Albrektsson, E., Rydholm, H., Rohss, K., Hassan-Alin, M., & Hasselgren, G. (2005). Tolerability, pharmacokinetics and effects on gastric acid secretion after single oral doses of the potassium-competitive acid blocker AZD0865 in healthy male subjects. *Gastroenterology* 128(4 Suppl. 2), A528.
- Nishida, A., Miyata, K., Tsutsumi, R., Yuki, H., Akuzawa, S., Kobayashi, A., et al. (1994). Pharmacological profile of (R)-1-[2,3-dihydro-1-(2'-methylphenacyl)-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-3-(3-methylphenyl)urea (YM022), a new potent and selective gastrin/cholecystokinin-B receptor antagonist, in vitro and in vivo. *J Pharmacol Exp Ther* 269, 725–731.
- Olbe, L., Carlsson, E., & Lindberg, P. (2003). A proton-pump inhibitor expedition: the case histories of omeprazole and esomeprazole. *Nat Rev Drug Discov* 2, 132–139.
- Park, S., Lee, S., Song, K., Lee, B., Kang, H., & Kang, J. (2003). The pharmacological properties of a novel acid pump antagonist, YH1885. *Gut* 52(Suppl. VI), A62.
- Parsons, M. E., & Keeling, D. J. (2005). Novel approaches to the pharmacological blockade of gastric acid secretion. *Expert Opin Investig Drugs* 14, 411–421.
- Pendley, C. E., Fitzpatrick, L. R., Capolino, A. J., Davis, M. A., Esterline, N. J., Jakubowska, A., et al. (1995). RP 73870, a gastrin/cholecystokinin-B receptor antagonist with potent anti-ulcer activity in the rat. *J Pharmacol Exp Ther* 273, 1015–1022.
- Piche, T., & Galmiche, J. P. (2005). Pharmacological targets in gastro-oesophageal reflux disease. *Basic Clin Pharmacol Toxicol* 97, 333–341.
- Rabon, E. C., McFall, T. L., & Sachs, G. (1982). The gastric [H,K]ATPase: H⁺/ATP stoichiometry. *J Biol Chem* 257, 6296–6299.
- Reuben, M. A., Lasater, L. S., & Sachs, G. (1990). Characterization of a β subunit of the gastric H⁺/K⁺-transporting ATPase. *Proc Natl Acad Sci U S A* 87, 6767–6771.
- Ritter, M., Schratzberger, P., Rossman, H., Wöll, E., Seiler, K., Seidler, U., et al. (1998). Effect of inhibitors of Na⁺/H⁺-exchange and gastric H⁺/K⁺ ATPase on cell volume, intracellular pH and migration of human polymorphonuclear leucocytes. *Br J Pharmacol* 124, 627–638.
- Sachs, G. (2001). Improving on PPI-based therapy of GORD. *Eur J Gastroenterol Hepatol* 13(Suppl. 1), S35–S41.
- Sachs, G., Chang, H. H., Rabon, E., Schackman, R., Lewin, M., & Saccomani, G. (1976). A nonelectrogenic H⁺ pump in plasma membranes of hog stomach. *J Biol Chem* 251, 7690–7698.
- Sachs, G., Scott, D. R., & Wen, Y. (2011). Gastric infection by *Helicobacter pylori*. *Curr Gastroenterol Rep* 13, 540–546.
- Sachs, G., Shin, J. M., Besancon, M., & Prinz, C. (1993). The continuing development of gastric acid pump inhibitors. *Aliment Pharmacol Ther* 7(Suppl. 1), 4–12 discussion 29–31.
- Sachs, G., Shin, J. M., & Howden, C. W. (2006). Review article: the clinical pharmacology of proton pump inhibitors. *Aliment Pharmacol Ther* 23(Suppl. 2), 2–8.
- Sachs, G., Shin, J. M., & Hunt, R. H. (2010). Novel approaches to inhibition of gastric acid secretion. *Curr Gastroenterol Rep* 12, 437–447.
- Sachs, G., Shin, J. M., Munson, K., & Scott, D. R. (2014). Gastric acid-dependent diseases: a twentieth-century revolution. *Dig Dis Sci* 59, 1358–1369.
- Sakurai, Y., Mori, Y., Okamoto, H., Nishimura, A., Komura, E., Araki, T., & Shiramoto, M. (2015a). Acid-inhibitory effects of vonoprazan 20 mg compared with esomeprazole 20 mg or rabeprazole 10 mg in healthy adult male subjects — a randomised open-label cross-over study. *Aliment Pharmacol Ther* 42, 719–730.
- Sakurai, Y., Nishimura, A., Kennedy, G., Hibberd, M., Jenkins, R., Okamoto, H., et al. (2015b). Safety, tolerability, pharmacokinetics and pharmacodynamics of single rising TAK-438 (vonoprazan) doses in healthy male Japanese/non-Japanese subjects. *Clin Transl Gastroenterol* 6, e94.
- Satoh, H. (2013). Discovery and development of proton pump inhibitors. In T., P., & H. (Eds.), *Proton Pump Inhibitors: A Balanced View*. Basel, Karger. *Front Gastrointest Res Vol.* 32. (pp. 1–17).
- Scarpignato, C., & Hunt, R. H. (2015). Editorial: towards extended acid suppression — the search continues. *Aliment Pharmacol Ther* 42, 1027–1029.
- Scarpignato, C., Kisfalvi, I., D'Amato, M., & Varga, G. (1996). Effect of dexlorglumide and spiroglumide, two new CCK-receptor antagonists, on gastric emptying and secretion in the rat: evaluation of their receptor selectivity in vivo. *Aliment Pharmacol Ther* 10, 411–419.
- Schwartz, C. (1900). Beiträge zur Pathologie und chirurgischen des penetrierenden Magenheeschwürren. *Mitt Grenzgeb Med Chir (Jena)* 5, 821–848.

- Scott, D. R., Besancon, M., Sachs, G., & Helander, H. (1994). Effects of antiseecretory agents on parietal cell structure and H/K-ATPase levels in rabbit gastric mucosa in vivo. *Dig Dis Sci* 39, 2118–2126.
- Scott, D. R., Helander, H. F., Hersey, S. J., & Sachs, G. (1993). The site of acid secretion in the mammalian parietal cell. *Biochim Biophys Acta* 1146, 73–80.
- Scott, D. R., Munson, K. B., Marcus, E. A., Lambrecht, N. W. G., & Sachs, G. (2015). The binding selectivity of vonoprazan (TAK-438) to the gastric H⁺,K⁺-ATPase. *Aliment Pharmacol Ther* 42, 1315–1326 Erratum in: *Alim Pharmacol Ther* 43, 315.
- Sekiguchi, M., Nagaya, H., Satoh, H., & Shino, A. (1992). Localization of a novel proton pump inhibitor, lansoprazole, in the gastric mucosa of the rat: a radioautographic study. *Acta Histochem Cytochem* 25, 405–410.
- Shin, J. M., & Kim, N. (2013). Pharmacokinetics and pharmacodynamics of the proton pump inhibitors. *J Neurogastroenterol Motil* 19, 25–35.
- Shin, J. M., & Sachs, G. (2006). Gastric H,K-ATPase as a drug target. *Dig Dis Sci* 51, 823–833.
- Shin, J. M., Besancon, M., Prinz, C., Simon, A., & Sachs, G. (1994). Continuing development of acid pump inhibitors: site of action of pantoprazole. *Aliment Pharmacol Ther* 8(Suppl. 1), 11–23.
- Shin, J. M., Inatomi, N., Munson, K., Strugatsky, D., Tokhtaeva, E., Vagin, O., & Sachs, G. (2011). Characterization of a novel potassium-competitive acid blocker of the gastric H,K-ATPase, 1-[5-(2-Fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1H-pyrrol-3-yl]-N-methylmethanamine monofumarate (TAK-438). *J Pharmacol Exp Ther* 339, 412–420.
- Shirai, N., Furuta, T., Xiao, F., Kajimura, M., Hanai, H., Ohashi, K., & Ishizaki, T. (2002). Comparison of lansoprazole and famotidine for gastric acid inhibition during the daytime and night-time in different CYP2C19 genotype groups. *Aliment Pharmacol Ther* 16, 837–846.
- Sippy, B. W. (1983). Landmark article may 15, 1915: gastric and duodenal ulcer. Medical cure by an efficient removal of gastric juice corrosion. By Bertram W. Sippy. *JAMA* 250, 2192–2197.
- Soll, A. H. (1982). Potentiating interactions of gastric stimulants on [¹⁴C]-aminopyrine accumulation by isolated canine parietal cells. *Gastroenterology* 83, 216–223.
- Soll, A. H., & Wollin, A. (1979). Histamine and cyclic AMP in isolated canine parietal cells. *Am J Phys* 237, E444–E450.
- Steel, K. (2002). Gastrin and gastrin receptor ligands — a review of recent patent literature. *Drugs* 5, 689–695.
- Takeuchi, K., Hirata, T., Yamamoto, H., Kunikata, T., Ishikawa, M., & Ishihara, Y. (1999). Effects of S-0509, a novel CCK_B/gastrin receptor antagonist, on acid secretion and experimental duodenal ulcers in rats. *Aliment Pharmacol Ther* 13, 87–96.
- Takinami, Y., Yuki, H., Nishida, A., Akuzawa, S., Uchida, A., Takemoto, Y., et al. (1997). YF476 is a new potent and selective gastrin/cholecystokinin-B receptor antagonist in vitro and in vivo. *Aliment Pharmacol Ther* 11, 113–120.
- Tsukimi, Y., Ushiro, T., Yamazaki, T., Ishikawa, H., Hirase, J., Narita, M., et al. (2000). Studies on the mechanism of action of the gastric H⁺,K⁺-ATPase inhibitor SPI-447. *Jpn J Pharmacol* 82, 21–28.
- Umegaki, E., Iwakiri, K., Hiramatsu, N., Sakurai, Y., Hori, T., Kudou, K., et al. (2014). A phase 3, randomized, double-blind, multicenter study to evaluate the efficacy and safety of TAK-438 (10 mg or 20 mg once daily) compared to lansoprazole (15 mg once daily) in a 24-week maintenance treatment for healed erosive esophagitis. *Gastroenterology* 146, S-738 T1052.
- Vagin, O., Denevich, S., & Sachs, G. (2003). Plasma membrane delivery of the gastric H,K-ATPase: the role of β-subunit glycosylation. *Am J Physiol Cell Physiol* 285, C968–C976.
- Wallmark, B., Briving, C., Fryklund, J., Munson, K., Jackson, R., Mendlein, J., ... Sachs, G. (1987). Inhibition of gastric H⁺,K⁺-ATPase and acid secretion by SCH28080, a substituted pyridyl(1,2a)imidazole. *J Biol Chem* 262, 2077–2084.
- Wedemeyer, R. S., & Blume, H. (2014). Pharmacokinetic drug interaction profiles of proton pump inhibitors: an update. *Drug Saf* 37, 201–211.
- Wolosin, J. M., & Forte, J. G. (1983). Kinetic properties of the KCl transport at the secreting apical membrane of the oxyntic cell. *J Membr Biol* 71, 195–207.
- Wurst, W., & Hartmann, M. (1996). Current status of acid pump antagonists (reversible PPIs). *Yale J Biol Med* 69, 233–243.
- Yao, X., & Forte, J. G. (2003). Cell biology of acid secretion by the parietal cell. *Annu Rev Physiol* 65, 103–131.
- Yu, K. S., Bae, K. S., Shon, J. H., Cho, J. Y., Yi, S. Y., Chung, J. Y., et al. (2004). Pharmacokinetic and pharmacodynamic evaluation of a novel proton pump inhibitor, YH1885, in healthy volunteers. *J Clin Pharmacol* 44, 73–82.
- Yuan, Y., Wang, C. C., Yuan, Y. -H., & Hunt, R. H. (2008). The proportion of patients who are free of reflux symptoms during the initial days of treatment with proton pump inhibitors (PPIs) in GERD trials: a meta-analysis. *Gastroenterology* 134(Suppl. 1), A-174.